SCIENTIFIC ABSTRACT

In the United States, it was estimated that 132,000 new cases of colorectal cancer will be diagnosed in 1998, and approximately 40% of those patients would eventually die from the disease. The liver is the most common site of metastases in advanced colorectal cancer. Mutations in the p53 suppressor gene have been reported in at least 75% of colorectal cancers. In vitro studies with human cancer cells have shown that delivery of wild-type p53 by SCH 58500 into cells previously mutant or null for p53 results in a dose-dependent inhibition of cell proliferation, frequently associated with cell death via apoptosis.

Currently, standard treatment for advanced colorectal cancer includes systemic chemotherapy (5-FU) and intrahepatic chemotherapy (FUDR). The response rate for chemotherapy is 20-60%. Patients with unresectable liver metastases have a survival of approximately 6-12 months. Standard chemotherapy is not curative. Further therapy for this disease is needed. The rationale for intrahepatic administration of SCH 58500 is based on the fact that disease commonly metastasizes to the liver, where the tumor(s) receive their blood supply solely from the hepatic artery. In addition, most patients have pre-existing immunity to adenovirus, resulting in rapid neutralization intravascularly. Regional delivery into the hepatic artery provides increased exposure to the tumor with minimal exposure to normal tissue outside the liver.

SCH 58500 is a recombinant adenoviral vector containing the cloned human wild-type (normal) tumor suppressor gene p53. The adenovirus has been rendered replication-deficient through deletion of the adenoviral E1 region. The design of this study incorporates the knowledge gained by the pre-clinical toxicology and pharmacology programs and Clinical Phase I studies. In 150 patients dosed to date using 3 different routes of administration (intrahepatic artery, intraperitoneal, and intratumoral), SCH 58500 has been well tolerated in Phase I. Based on the Phase I shedding data, we believe SCH 58500 to be safe to the environment and health care workers. Transgene expression has been consistently seen, by RT-PCR, in post-dosing tissue biopsies. The risk benefit ratio favors the potential for clinical effect.

The objective of the study is to confirm that p53 in addition to standard chemotherapy is superior to chemotherapy alone. The target patient population for this trial is patients with colorectal cancer metastatic to the liver. All patients will receive standard chemotherapy with half of the patients randomized to receive the experimental p53 product in combination with the chemotherapy. This is a randomized, open label, multicenter trial to be conducted worldwide.